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The Accuracy and Clinical Feasibility of a New Bayesian-Based Closed-Loop Control System for Propofol Administration Using the Bispectral Index as a Controlled Variable

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BACKGROUND: Closed-loop control of the hypnotic component of anesthesia has been proposed in an attempt to optimize drug delivery. Here, we introduce a newly developed Bayesian-based, patient-individualized, model-based, adaptive control method for bispectral index (BIS) guided propofol infusion into clinical practice and compare its accuracy and clinical feasibility under direct observation of an anesthesiologist versus BIS guided, effect compartment controlled propofol administration titrated by the anesthesiologist during ambulatory gynecological procedures.
METHODS: Forty ASA patients were randomly allocated to the closed-loop or manual control group. All patients received midazolam 1 mg IV and alfentanil 0.5 mg IV before induction. In the closed-loop control group, propofol was administered using the previously described closed-loop control system to reach and maintain a target BIS of 50. In the manual control group, the propofol effect-site concentration was adapted at the discretion of the anesthesiologist to reach and maintain a BIS as close as possible to 50. Induction characteristics, performance, and robustness during maintenance and recovery times were compared. Hemodynamic and respiratory stability were calculated as clinical feasibility parameters.
RESULTS: The closed-loop control system titrated propofol administration accurately resulting in BIS values close to the set point. The closed-loop control system was able to induce the patients within clinically accepted time limits and with less overshoot than the manual control group. Automated control resulted in beneficial recovery times. Our closed-loop control group showed similar acceptable clinical performance specified by similar hemodynamic, respiratory stability, comparable movement rates, and quality scores than the manual control group.
CONCLUSIONS: The Bayesian-based closed-loop control system for propofol administration using the BIS as a controlled variable performed accurate during anesthesia for ambulatory gynecological procedures. This control system is clinical feasibility and can be further validated in clinical practice.
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Closed-loop control of the hypnotic component of anesthesia has been proposed in an attempt to optimize drug delivery.[1] Various automated drug delivery systems have been described in the literature using spontaneous electroencephalogram[2–10] or auditory evoked potential indices[11] as controlled variables. However, several limitations such as lack of control during induction, exclusion of already anesthetized patients when applying model-based controllers, and problems dealing with patient variability during control have been encountered in previous work. Outside anesthesia, adaptive control has been well used in medicine for decades, for example, to control nitroprusside infusions.[12]

Our group has developed a new model-based patient-individualized closed loop control system for propofol administration using the bispectral index (BIS) as a controlled variable taking care of these limitations by implementing Bayesian methodology. Recently, we have applied simulations to select these Bayesian variances yielding the optimal controller for this Bayesian-based control system.[13] Bayesian optimization, as proposed by Sheiner and

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Michel MRF Struys, MD, PhD, Tom De Smet, MSc, and Steven L. Shafer, MD, are patent holders of the "model-based" closed-loop system. The new controller framework has been published in detail in the patent application WO 2005/072792 A1 (see http://www.wipo.int/pctdb/en/search-adv.jsp). Aspect Medical Systems (Norwood, MA) is the applicant in all countries except United States.

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coworkers,[14] individualize the pharmacodynamic relationship by combining individual information with the knowledge of an *a priori* probability density function containing the statistical properties of the parameter to be estimated.[15] The Bayesian method starts from a standard, population-based response model providing the prior distribution of parameter values. These values are adjusted to reflect the patient's own parameters over time, based on the observed response of the individual patient under varying circumstances. This process makes use of specific modeling weights, called Bayesian variances, which determine how the patient-specific model can deviate from the population model. These Bayesian variances need to be optimized for control performance in a target population, which was done for this controller and described in previous work.[13]

The aim of this study was to introduce this newly developed system into clinical practice and compare its accuracy and clinical feasibility under direct observation of an anesthesiologist versus BIS guided, effect compartment controlled propofol administration titrated by the anesthesiologist during ambulatory gynecological procedures. The main novelty in this investigation compared with the referenced studies is that the new control system enables us to include the induction phase in the closed-loop control mode of the controller rather than only the maintenance phase.

METHODS

System Specifications

Controlled Variable, Data Management, and Actuator Control

The BIS was applied as controlled variable to titrate propofol administration. BIS (BIS-XP®, version 4) is derived from the frontal electroencephalogram as calculated by the A-2000 BIS® Monitor (Aspect Medical Systems, Inc., Norwood, MA) using four BIS-Sensor electrodes (Aspect Medical Systems).

In all patients, our setup used a laptop running RUGLOOPII[1]* to calculate the target controlled infusion (TCI) algorithms to steer the infusion pump, and to record all relevant physiologic data including the BIS signal. The target controlled infusion system used a three compartment model with an effect compartment, previously published by Schnider et al.[16,17] As in a previous study of Struys et al.,[18] for the calculation of the propofol effect-site concentration (CePROP) a fixed time-to-peak effect site concentration[19] of 1.6 min was used, as also published by Schnider et al.[17]

In the closed-loop control group, the RUGLOOPII platform also executed the closed-loop control, calculating an adequate propofol effect-site concentration from the measured BIS, to serve as the input to the effect compartment controlled TCI system. In the control group, the anesthetist applied the TCI system directly to titrate the propofol administration.

Blood pressure, heart rate, end-tidal CO_2, and Spo_2 were acquired using the S5-monitor. (GE Healthcare, Helsinki, Finland.). All data were stored on hard disk at a 5-s interval.

Closed-Loop Controller

The closed-loop control algorithm attempts to minimize the error between the measured BIS value and the target BIS value selected by the anesthesiologist by calculating an adequate propofol effect-site concentration using a patient-individualized, model-based, adaptive control method. The applied model-based adaptive control system with Bayesian model optimization is described extensively in our previous work.[13]

The controller is based on a pharmacodynamic model represented by a patient-individualized sigmoid E_{max} model, describing the relation between BIS and CePROP, and characterized by four parameters: E_0 equals the BIS value at no drug effect; E_{max} equals the change in BIS between no drug effect and maximum drug effect; EC_{50} represents the CePROP at 50% of effect; and γ represents the steepness of drug effect around 50%. The model can be presented as:

$$\mathrm{BIS} = E_0 - (E_0 - E_{max}) * \left(\frac{\mathrm{CePROP}^{\gamma}}{\mathrm{CePROP}^{\gamma} + \mathrm{EC}_{50}{}^{\gamma}} \right) \quad (1)$$

The controller estimates the target propofol effect-site concentration that will minimize the difference between measured and target value for the controlled variable (BIS) by shifting the sigmoid E_{max} model along the propofol effect-site concentration axis. A detailed explanation of this "moving curve controller" can be found in our previous work.[10]

Originally, the patient-specific sigmoid E_{max} curve was estimated during induction and used unchanged throughout the case. Recently, the model estimator was improved by implementing a Bayesian technique to continuously calculate a patient-individualized sigmoid E_{max} combining an initial population mean model with the observed responses over the entire course of the anesthetic. The development of and the estimation of the optimal modeling weights for this Bayesian-based closed loop control system were

*RUGLOOP II, written by Tom De Smet, MSc (medical engineer, DEMED Engineering, Temse, Belgium) and Michel MRF Struys, MD, PhD(Professor of Anesthesia, Ghent University, Gent, Belgium) More information available at http://www.anesthesia-uzgent.be, latest accessed on August 23, 2007.

reported previously.[13] Generally, the Bayesian objective function looks like:

$$\sum \frac{(\mathrm{BIS}_{\mathrm{sample}} - \mathrm{BIS}_{\mathrm{estimated}})^2 * \mathrm{MAX}\left[\left(1 - \left[\frac{(t - t_{\mathrm{sample}})}{\mathrm{sample}_{\mathrm{TO}}}\right]^2\right);0\right]}{\mathrm{VAR}^2_{\mathrm{samples}}}$$
$$+ \frac{(\mathrm{EC}_{50,\mathrm{Population}} - \mathrm{EC}_{50,\mathrm{Estimated}})^2}{\mathrm{VAR}^2_{\mathrm{EC}_{50}}} + \frac{(\gamma_{\mathrm{Population}} - \gamma_{\mathrm{Estimated}})^2}{\mathrm{VAR}^2_{\gamma}}$$
$$+ \frac{(D_{\mathrm{Population}} - D_{\mathrm{Estimated}})^2}{\mathrm{VAR}^2_{D}} \quad (2)$$

whereby $\mathrm{BIS}_{\mathrm{sample}}$ is the observed value and $\mathrm{BIS}_{\mathrm{estimated}}$ is the estimated value based on the model to be fitted. EC_{50} and γ are the nonfixed terms of the sigmoid $E_{\max}$ model, "Population" is the original population reference model parameter (=*a priori* information), and "Estimated" is the estimated value of parameter for the individual. SampleTO is a forgetting factor representing the samples taken into account for the modeling on a time-limited base, and D is the systems delay to be estimated.

Clinical Study

After Institutional Ethics Committee (Ethics Committee of the Ghent University Hospital, Gent, Belgium) approval, informed consent was obtained from 40 ASA I and II female patients, aged 18–45 yr, scheduled for ovum retrieval, whereby ovocytes are collected from the follicles in the ovaries by aspiration using ultrasonic-guided needle puncture through the vaginal wall. They were randomly (permuted block randomization, blocks of 4, 20 patients per group) allocated to the closed-loop or manual control group. Exclusion criteria included weight <70% or more than 130% of ideal body weight, neurological disorder, and use of psychoactive medication including alcohol. All patients received midazolam 1 mg IV 7 min and alfentanil 0.5 mg IV 2 min before induction with propofol. All drugs were administered via a large left forearm vein. Every patient received about 300 mL of crystalloid fluid during the study period. No fluid load was given before induction. No other drugs were given, except paracetamol 1 g IV at the end of the procedure to provide postoperative pain relief. All patients maintained spontaneous ventilation via a facemask delivering oxygen 6 L/min.

In the closed-loop control group, propofol was administered using the previously described closed-loop control system. To start and maintain propofol administration, the requested BIS target was fixed at 50 for the complete duration of the case. In the manual group, propofol was administered using the effect compartment controlled TCI system (RUGLOOP). The initial target propofol effect-site concentration was set at 5.0 μg/mL, which was exactly similar to the initial EC_{50} in the initial population model in the closed-loop controller. The propofol target concentration was adapted at the discretion of the anesthesiologist (the same person in all cases) to maintain a BIS as close as possible to 50.

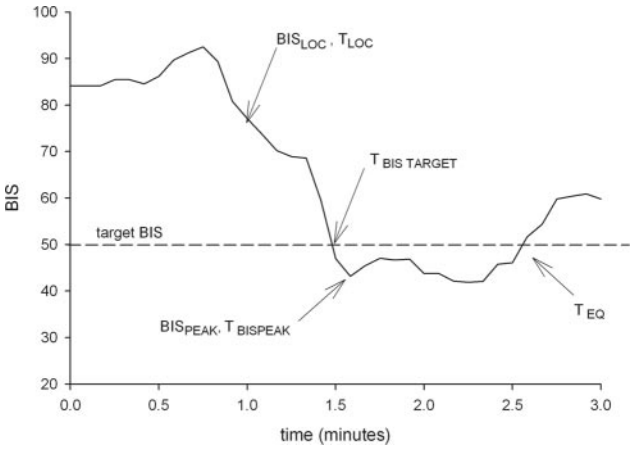

Figure 1. Schematic representation of performance during induction. T_{LOC} = moment of loss of consciousness, $\mathrm{BIS}_{\mathrm{LOC}}$ = BIS at the moment of loss of consciousness, $T_{\mathrm{BIS\ TARGET}}$ = observed time required for reaching the target BIS value, $T_{\mathrm{PEAK,\ BIS}}$ = observed time required for reaching maximal drug effect (lowest BIS value), $\mathrm{BIS}_{\mathrm{PEAK}}$ = observed BIS value at $T_{\mathrm{PEAK,\ BIS}}$, T_{EQ} = observed time required for reaching the target value after the initial overshoot, also called time to steady-state.

The time and BIS were recorded at the moment of LOC. We also calculated the propofol dose used for the entire procedure. Heart rate, end tidal CO_2, Spo_2, and BIS were acquired every 5 s. Artifacts in the BIS due to poor signal quality were automatically detected and excluded from further analysis. Blood pressure was acquired every 1 min. RUGLOOP II digitally recorded all vital signs and infusion data. During the case, incidents of spontaneous movement were documented.

At the end of surgery (i.e., end of surgical stimulus), propofol administration was stopped and recovery parameters (time until opening eyes, and time until saying name and date of birth) were recorded.

Evaluation of the Control Performance

The evaluation methods of the control performance were described and applied previously.[10] BIS was defined as the controlled variable in both groups and the BIS target value was set at 50 in both groups. Controller performance metrics are calculated on the measured values of the controlled variable versus its target value. The performance metrics of the closed-loop and manual control group was evaluated and compared during induction, maintenance, and recovery.

We recorded time until LOC from the start of propofol infusion and the amount of propofol used during induction. The control performance during induction was studied taking into account the following parameters (Fig. 1):

- $\mathrm{BIS}_{\mathrm{LOC}}$ = BIS at the moment of loss of consciousness.
- $T_{\mathrm{BIS\ TARGET}}$ = observed time required for reaching the target BIS value.

- $T_{PEAK,\ BIS}$ = observed time required for reaching maximal drug effect (lowest BIS value).
- BIS_{PEAK} = observed BIS value at $T_{PEAK,\ BIS}$.
- T_{EQ} = observed time required for finally reaching the target value with or without overshoot, also called time to steady-state.

The control performance on the controlled variable (BIS) was calculated for each patient from the start until termination of propofol administration using the following performance metrics.

First, we evaluated the percentage of case time the BIS remained between 40–60 and 45–55. An important derivative metric is the percentage of time with too low BIS (lower than 40 or 45, respectively) or too high BIS (higher than 60 or 55, respectively).

Additionally, the performance-error based method of Varvel et al.[20] was applied. Using all observations within the period, the performance error (PE) was calculated according to Equation 2.

$$\mathrm{PE} = \frac{(\text{measured value} - \text{target value})}{\text{target value}} * 100 \qquad (3)$$

Subsequently, for each patient bias (median prediction error [MDPE]), inaccuracy (median absolute performance error [MDAPE]), divergence and wobble were calculated:

- MDPE is a measure of bias and describes whether the measured values are systematically either above or below the target value. MDPE was calculated from

$$\mathrm{MDPE}_i = \mathrm{median}\{\mathrm{PE}_{ij},\quad j = 1, \ldots, N_i\} \qquad (4)$$

where N_i is the number of values PE obtained for the i-th subject.

- MDAPE reflects the inaccuracy of the control method in the i-th subject:

$$\mathrm{MDAPE}_i = \mathrm{median}\{|\mathrm{PE}|_{ij},\quad j = 1, \ldots, N_i\} \qquad (5)$$

where N_i is the number of values 231 PE obtained for the i-th subject.

- Divergence describes the possible time-related trend of the measured effects in relationship to the targeted values. It is defined as the slope of the linear regression equation of PE against time and is expressed in units of percentage divergence per minute. A positive value indicates progressive widening of the gap between targeted and measured values, whereas a negative value reveals that the measured values converge on the predicted values.
- Wobble is another index of the time-related changes in performance and measures the intrasubject variability in performance errors. In the i-th subject, the percentage of wobble is calculated as follows:

$$\mathrm{wobble}_i = \mathrm{median}\{|PE_{ij} - \mathrm{MDPE}_i|,\quad j = 1, \ldots, N_i\} \qquad (6)$$

Additionally, we compared hemodynamic (heart rate and mean arterial blood pressure) and respiratory (oxygen saturation) stability from start until termination of the propofol administration between groups. For heart rate, we evaluated the percentage of case time heart rate remained between 50 and 90 bpm. As such, the percentage of time with bradycardia (lower than 50 bpm) or tachycardia (higher than 90 bpm) was calculated too. For mean arterial blood pressure, we evaluated moderate and severe hypotension indicated by the percentage of case time the blood pressure went below 60 and 50 mm Hg, respectively, and hypertension defined by a blood pressure values above 135 mm Hg.[21]

During recovery, we compared the time from stop propofol infusion until opening of the eyes on command and orientation. Hereby, orientation was defined as saying name and date of birth on request. The commands for opening of the eyes and orientation were repeated every 10 s until positive.

In these clinical procedures, patients are allowed to move smoothly with feet or hands, however, no movement of the upper legs nor pelvis is allowed as this might result in dangerous malpositioning of the needle during the retrieval procedure. Therefore, incidence (number of patients) of allowed and not allowed movements was recorded. Additionally, we asked the gynecologist at the end of the procedure to score the overall patients' anesthetic condition between 0% and 100%, whereby 0 means very unsafe to work and 100 means perfect.

Statistical Analysis Used

Power calculations were based on previous studies.[10] For control, overshoot at induction and MDAPE are important endpoints. For overshoot at induction, Struys et al.[10] found a difference in BIS_{PEAK} of 6 BIS units with a standard deviation of 4. On the basis of this, 12 patients would be required to show a difference between groups with a type I and II error of 5%. For MDAPE, a 30% better result for closed-loop control versus manual control with a standard deviation of 25% in both groups would be revealed with a type I and II error of 5% when studied 18 patients per group. As such, we included 20 patients per group to reveal accurate power.

Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL). Data are presented as mean ± SD or as median (range). All data were checked for Gaussian distribution by the method of Kolmogorov and Smirnov. Differences between groups were analyzed by a Student's t-test or Mann–

Table 1. Demographic Data

	Closed-loop control ($n = 20$)	Manual-control ($n = 20$)
Age (yr)	31.6 ± 5.3	32.5 ± 5.0
Height (cm)	165.0 ± 5.9	168.8 ± 5.5
Weight (kg)	62.2 ± 9.0	65.4 ± 8.0

Table 2. Clinical Data

	Closed-loop control	Manual-control ($n = 20$)
Induction time (s)	66 ± 25*	49 ± 9*
Propofol dose until LOC (mg)	91 ± 22*	106 ± 10*
BIS_{LOC}	73 ± 11*	82 ± 7*
Duration of anesthesia from start until stop propofol infusion (s)	1013 ± 191	1031 ± 239
Total propofol used (mg)	261 ± 68	292 ± 67
BIS at stop propofol administration	46 ± 5	43 ± 11
CePROP at stop propofol administration	3.1 ± 0.8	3.5 ± 0.9
Recovery time until opening of the eyes (s)	215 ± 133*	316 ± 125*
Recovery times until orientation (s)	259 ± 128*	343 ± 112*

BIS = bispectral index; LOC = loss of consciousness; CePROP = propofol effect-site concentration.

* $P < 0.05$ between groups.

Whitney test, depending on their distribution. Categorical data (movement) were analyzed by a χ^2 test.

Evaluation of Bayesian Functionality

The addition of the Bayesian optimization adds complexity to the control system. This added complexity can only be justified if, at least, the parameters calculated by the Bayesian optimization for the individual patient deviate from the typical values. This comparison was realized by comparing graphically the difference in model EC_{50} and delay, target effect site concentration change calculated by the controller using the Bayesian-optimized model versus a hypothetical controller using the unchanged typical values, as well as the time integration of the latter one.

RESULTS

Similar population demographics were found between groups for age, weight, and height (Table 1). No patients were excluded and all data captured by the recording system were included in the analysis. The observations made at LOC are listed in Table 2. Some longer induction times are noticed in the closed-loop control group. Other clinical parameters during induction revealed some statistical differences without clinical relevance. Times until first surgical stimulus (not shown), duration of anesthesia, and total amount of propofol used were similar in both groups. The performance of the hypnotic control using BIS during the induction phase is shown in Table 3. Although slower induction time was observed, similar times to reach the target BIS were found in the closed-loop control group than the manual control group. However, the duration and magnitude of the initial overshoot in BIS below target was less pronounced in the closed-loop control group than the manual control group.

Table 3. Control Quality and Safety During Induction and Maintenance

	Closed-loop control	Manual-control
$T_{BIS\ TARGET}$ (s)	93 ± 34	89 ± 64
BIS_{peak}	40 ± 7*	33 ± 10*
$T_{PEAK,\ BIS}$ (s)	125 ± 61	148 ± 112
T_{EQ} (s)	176 ± 101	204 ± 124[a]
% of time BIS between 40 and 60	75 ± 13*	43 ± 17*
% of time BIS between 45 and 55	47 ± 13*	20 ± 16*
% of time BIS lower than 40	15 ± 12*	48 ± 17*
% of time BIS lower than 45	39 ± 12*	69 ± 17*
% of time BIS higher than 60	9 ± 3	9 ± 4
% of time BIS higher than 55	13 ± 3	11 ± 6
% of time HR between 50 and 90 beats/min	100 (6)[b]	100 (10)[b]
% of time HR lower than 50 beats/min	0 (0)[b]	0 (0)[b]
% of time HR higher than 90 beats/min	0 (6)[b]	0 (10)[b]
% of time MAP lower than 60 mm Hg	6 (78)[b]	6 (87)[b]
% of time MAP lower than 50 mm Hg	0 (0)[b]	0 (3)*
% of time MAP higher than 135 mm Hg	0 (0)[b]	0 (0)[b]

$T_{BIS\ TARGET}$ = observed time required for reaching the target bispectral index (BIS) value; BIS_{PEAK} = observed BIS value at $T_{PEAK,\ BIS}$; $T_{PEAK,\ BIS}$ = observed time required for reaching maximal drug effect (lowest BIS value); T_{EQ} = observed time required for reaching the target value after the initial overshoot; HR = heart rate; MAP = mean arterial blood pressure.

[a] Only 16 out of the 20 patients returned to BIS target during the entire case.

[b] These data are presented as median (range).

* $P < 0.05$ between groups.

The trajectory of BIS between start and termination of propofol (=the real duration of control) for all individual patients accompanied by the average value for the group versus time is plotted in Figure 2. As observed in parts A and B, significant lower BIS values and more interindividual variability were found in the manual control group, leading to a significant worse prediction error over time (parts C and D). Figures 3E and F shows the individual and averaged CePROP between start and termination of propofol administration. It can be noticed that during and shortly after induction, the CePROP was lower in the closed-loop control group than manual control group. Additionally, Table 3 proves that the percentages of case time with accurate BIS control was significantly better in

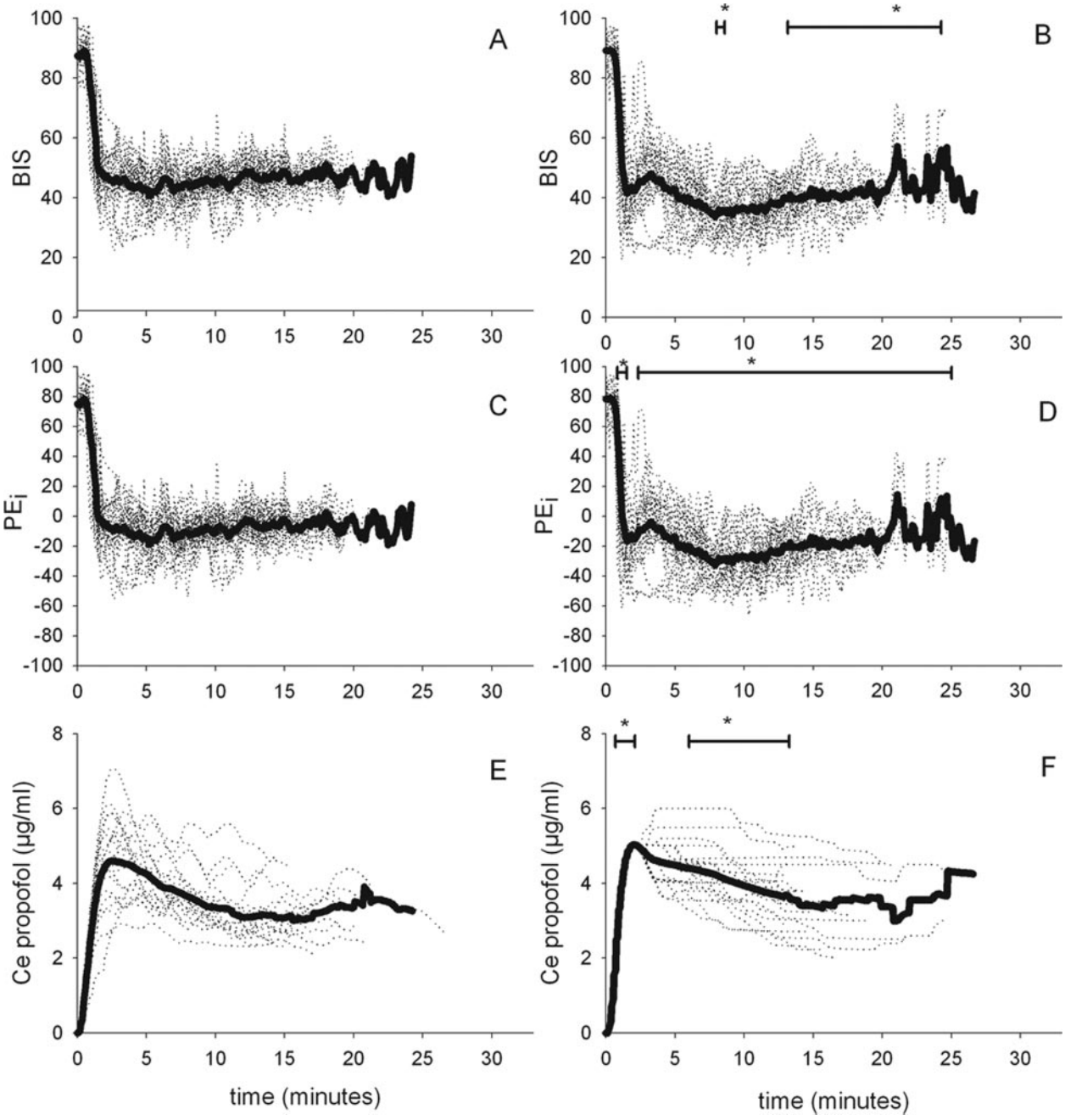

Figure 2. Individual (dotted line) and average (fat line) bispectral index (BIS), performance error (PE), and propofol effect-site concentration (CePROP) for closed-loop control (parts A, C, and E) and manual control (parts, B, D and F) group. For each patient, data are represented from start (time = 0) until stop of the propofol administration. - and * indicates the time period during the case that showed significance ($P < 0.05$) between groups.

the closed-loop control group compared with the manual group. Significant differences were due to more too low BIS values in the manual control group. The overall performance of control for BIS is shown in Table 4. Performances are calculated from start to stop of the propofol infusion, except for divergence, which was analyzed from the moment of $T_{\text{BIS TARGET}}$ until stop of the propofol administration. It was chosen to use $T_{\text{BIS TARGET}}$ rather than T_{EQ} as, in the manual control group, not all patients reached the target BIS again. The overall better performance of BIS control in the closed-loop control group is also proven by analyzing the PE, MDPE, MDAPE, divergence, and wobble, which revealed all more advantageous results for the closed-loop control group compared with the manual control group.

Hemodynamic stability was similar in both groups without dangerous alterations due to inaccurate control. Similar trends in heart rate were found during the cases in both groups (Figs. 3A and B). No long-lasting incidences of brady- or tachycardia were noticed (Table 3). As shown in Figure 3 (C and D), lower blood pressures were observed in the closed-loop control group compared with the manual control group between 300 and 600 s from the start of the propofol administration. However, this did not result in a

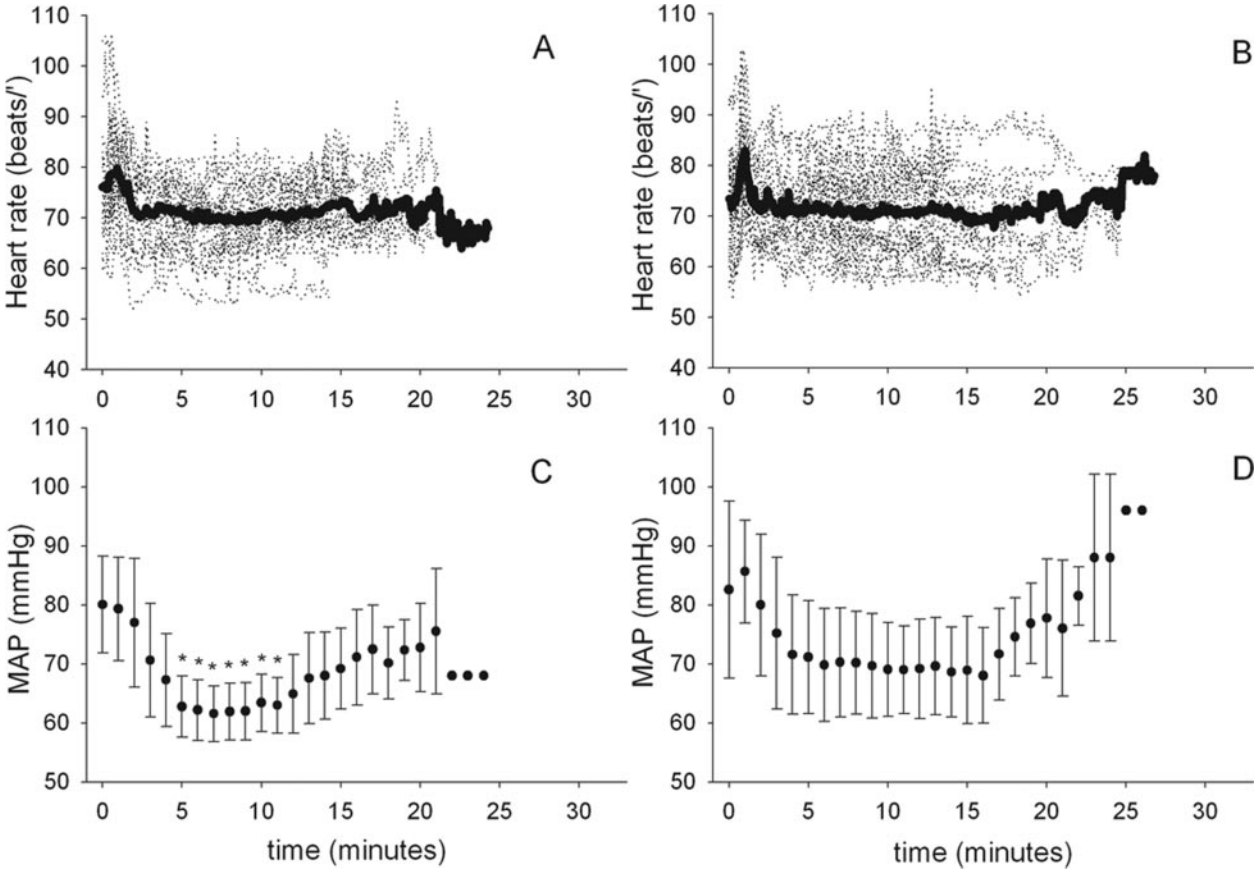

Figure 3. Individual (dotted line) and average (fat line) heart rate from start until stop of the propofol administration for the closed-loop control (A) and manual control (B) group. Mean arterial blood pressure (MAP) (mean ± SD) for closed-loop control (C) and manual control (D) group. *$P < 0.05$ between groups.

Table 4. Performance of Control for BIS From Start Until Termination of Propofol Administration

	Closed-loop control	Manual-control
Average PE (%)	−2.91 ± 24.49*	−14.17 ± 28.88*
MDPE (%)	−7.78 ± 3.46*	−19.96 ± 8.38*
MDAPE (%)	11.51 ± 4.0*	24.06 ± 8.01*
Divergence (% min)	−0.009 ± 0.012[a]	0.004 ± 0.025[a]
Wobble (%)	8.44 ± 2.84*	11.48 ± 4.19*

PE = prediction error; MDPE = median prediction error; MDAPE = median absolute performance.

[a] Divergence was calculated between the moment of $T_{BIS\ TARGET}$ until termination of the propofol infusion.

* $P < 0.05$ between groups.

higher incidence of moderate nor severe hypotension (Table 3). No episodes of hypertension were observed in both groups (Table 3). No patients had respiratory depression leading to a drop in saturation (data not shown).

At the end of the procedure, propofol administration was stopped. BIS and CePROP were similar between groups at the end of the propofol administration. Recovery times were recorded. As shown in Table 2, times until opening of the eyes and orientation were significantly shorter in the closed-loop control group than the manual control group.

Movements were recorded. In the closed-loop control group, 7 patients showed allowed and 4 not allowed movements. In the manual control group, 3 patients showed allowed and 5 showed not allowed movements. None of these events leaded to complications other than shortlasting interruption of the retrieval procedure. In the closed-loop control group, overall quality of anesthesia received a 94% (11%) score compared with a 89% (17%) score in the manual control group.

Figure 4 demonstrates the functionality of the Bayesian modeling. Parts (A) and (B) show a clear change over time of the calculated EC_{50} and estimated delay. As γ is not estimated, it has a constant value, as well as E_0 and E_{MAX} (not shown).

More illustrative than the covariate values is the difference in control behavior, represented in Figures 4C and D. Part C demonstrates the control action that was executed by the controller using the Bayesian-optimized curve, compared with a hypothetical controller that would use the unchanged typical values (Part D). Unlike pharmacokinetic datasets, a closed-loop control dataset cannot be compared against multiple control algorithms since the *post hoc* calculated control actions cannot have a real effect on the patient. Each sample point in Figure 4D therefore should be regarded as an instantaneous hypothetical control to be applied on the patient's state realized by the control history of the original controller. Consequently, all controllers with identical steady-state

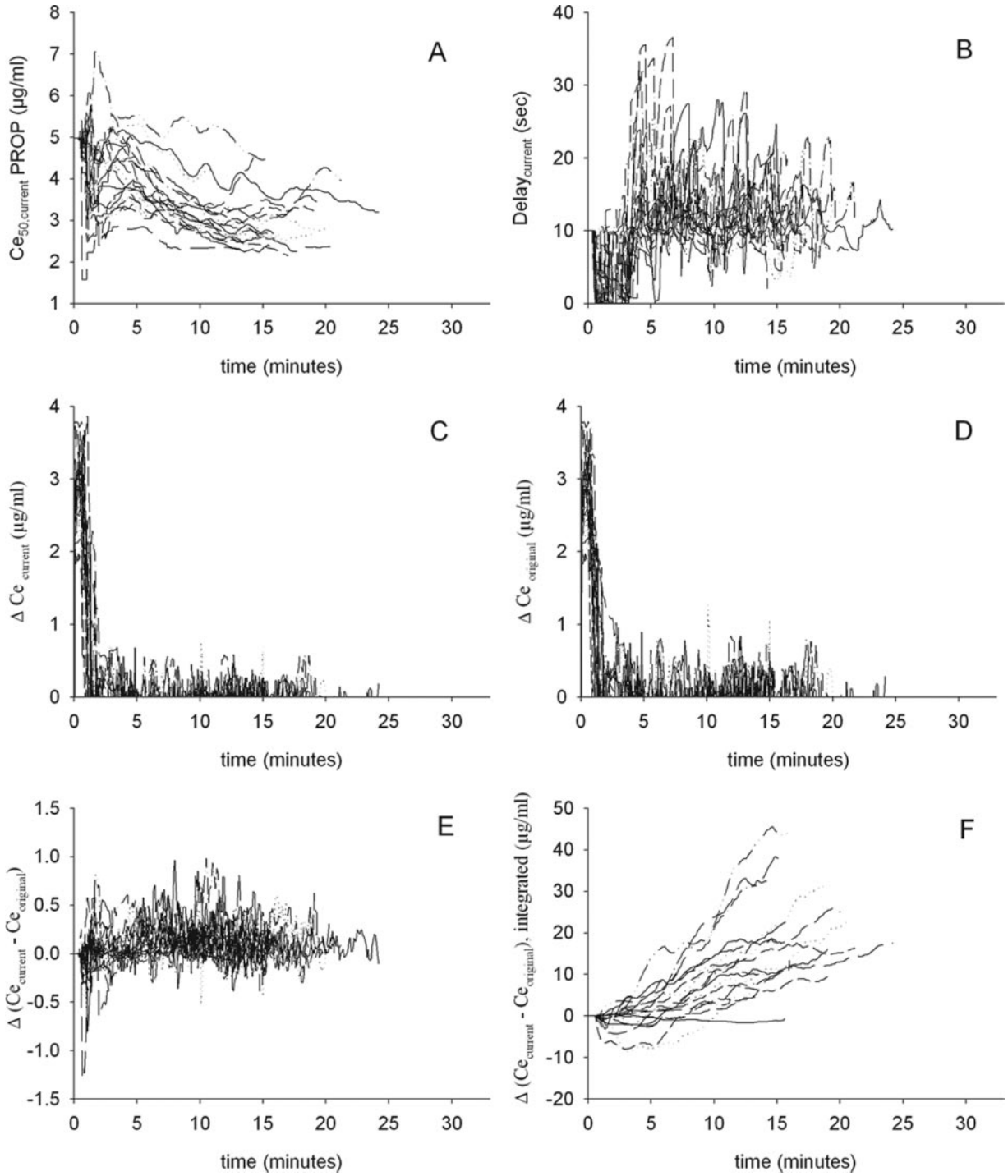

Figure 4. Functionality of the Bayesian modeling. Parts (A) and (B) show the change over time of the calculated EC_{50} and estimated delay. Part C demonstrates the control action that was executed by the controller using the Bayesian-optimized curve, compared with a hypothetical controller that would use the unchanged typical values (Part D). Part E plots the difference between these control actions to enlarge the scale. Part F shows the integration over time (F) to demonstrate the cumulative difference of the data points shown in part E.

behavior will show an average control difference close to zero most of the time. Part E plots the difference between these control actions to enlarge the scale. To verify the net effect of the control difference, the control differences were integrated over time (Part F) demonstrating the cumulative control difference.

DISCUSSION

It was hypothesized that the implementation of Bayesian technology into our previously described and validated[3] patient-individualized, adaptive, model-based closed-loop control system would allow us to overcome previous limitations of existing systems hereby guaranteeing clinical feasibility and accuracy. We found

that our closed-loop control system titrated propofol administration accurately resulting in BIS values close to the set point. The closed-loop control system was able to induce the patients within clinically accepted time limits and with less overshoot than the manual control group. Automated control resulted in beneficial recovery times. Our closed-loop control group showed acceptable performance compared to the manual control group specified by similar hemodynamic, respiratory stability, comparable movement, and quality scores.

The design of this investigation was carefully considered. In previous work from our group,[10] some of our methodology was criticized as propofol was titrated manually in our control group to achieve set points that are commonly used during anesthesia, i.e., blood pressure, heart rate, and sympathetic tone while using BIS in the closed-loop control group.[22] Therefore, in this study, we allowed the clinician to see and use the BIS online and to use similar TCI algorithm and titration limits as the closed-loop control system in order to approach the closed-loop control group methodology as close as possible. Although our closed-loop control system would have been able to compensate for interindividual variability, we aimed at studying a very homogenous patient population. As a result, the only real difference between the two study populations was the automated or manual control of the hypnotic component of anesthesia. As stated in an editorial by Glass and Rampil,[22] it is important to underline the critical role of analgesia in the performance of hypnotic control. High dosages of opiates will dampen the arousal effects caused by a noxious stimulus[23] hereby requiring much smaller adjustments in propofol concentration. As the ovum retrieval procedure only requires a small dose of opiates, the performance of control was not influenced by high opiate concentrations. The noxious stimuli during this procedure are very homogeneous in all patients. Additionally, as all patients were aimed at breathing spontaneously and could move during the procedure, this introduced a lot or performance challenges for both human and automated control.

This closed-loop controller is able to manage both induction of anesthesia and pharmacodynamic changes during the case. This is due to the application of the Bayesian optimization technology. For the induction, we showed that our closed-loop control system performed better compared with the manually induced patients with similar times to reach the set point but with less overshoot and faster return to the set point after the initial overshoot, even though both the closed-loop controller and the clinician in the manual control group started with a same CePROP target of 5 μg/mL. The beneficial results for closed-loop control are due to the fact that the closed-loop controller will correct faster (even during the bolus) when individual patient drug response (BIS change) becomes available while a human operator will "wait and see" before he or she corrects.

During maintenance, the clinical performance goal of any control system, both human and automated, is to provide tight control. For BIS, adequate levels of control were defined as having a BIS value within ± 10 BIS units of the set point.[3] Table 3 demonstrates that closed-loop control offered accurate control during significantly more percentages of case time. Hereby, it is important to state that the analyzed time period starts and stops at start and termination of propofol administration, so includes the induction phase. In this study, induction is an integral part of the control period and included in the analysis. In the manual control, it can be observed that a too deep level of anesthesia caused worse control.

Additionally, robustness of the controller should be proven. O' Hara and colleagues[24] proposed the goals of control in anesthesia as (1) keeping the average value of the controlled variable within defined limits; (2) minimizing oscillations in the controlled variable within these limits, and (3) guaranteeing stability so that over time the size of the oscillations either becomes smaller or remains constant at an acceptable level, rather than increasing. A mathematical interpretation of these criteria can be found in Varvel and co-workers[20] for computer-controlled infusion pumps, which can be applied on closed-loop controller performance after minor modifications.[3] As observed in Table 4 and Figure 2, overall and time specific PE's were significantly better in the closed-loop than manual control group. All derived performance parameters (MDPE, MDAPE, divergence, and wobble) were significantly better in our closed-loop control group compared with the manual control group.

Hereby, it is important to underline that the results of the closed-loop controller are clinically acceptable alone, even without comparing it with a manually controlled group. The performance results from the manual control group can be used to have an idea of the performance of the trained clinician and as such, to compare absolute performance values. MDPE indicates the bias of the controller without revealing any information neither on dynamic or higher-frequency behavior nor on the amplitude of possible oscillations in control. Note that MDPE is a signed value and thus represents the direction (over- or underprediction) of the performance errors rather than the size of the errors, which is represented by MDAPE. Even though MDAPE does not indicate the sign of a possible bias, it describes both the amplitude of possible bias as well as all other errors that prevent the controller from approaching the control target. Note that in MDPE is negative when applying our closed-loop control system, which indicates that the system tend to overdose, leading to BIS levels below target. This can be attributed to the fact that closed-loop control for drug delivery performs, in essence, an asymmetric control operation. They only govern the infusion, not the

elimination of drug from the body, which is a slower process. This phenomenon has been observed in our earlier studies as well.[10] Divergence and wobble indicates to the oscillation of the controller behavior (wobble) and the tendency of the controller to converge on the target over a longer time (divergence). A negative divergence number indicates convergence to the target. The absolute value indicates the speed of convergence or divergence. As shown in Table 4, the divergence in the closed-loop control group shows an average negative number in contrast to the manual control group. A careful interpretation of Figure 2D shows that, after initially reaching the target, the manual control group drifts to significantly lower BIS values needing more time to correct. This episode might remain dominant in the divergence number, falsely suggesting that control in the manual control group will keep on diverging. This, obviously, does not reduce the significance of the negative divergence in the control group.

Whereas model based adaptive control is not new, the integration of Bayesian methods for model estimation is a new method. The Bayesian approach starts out using population based parameter values and individualizes them according to knowledge acquired about the specific patient during treatment. As a clear deviation is seen between the controller based on the Bayesian-estimated curve and a hypothetical controller using the unchanged typical values, the added complexity is justified.

The net positive sum in Figure 4F demonstrates that, on average, the Bayesian controller causes a faster response for drug increase than the original controller, except for one patient where the accumulated difference remains close to zero.

The change in typical value is apparent for the ce50 and delay, which are estimated in the Bayesian approach. Despite of γ being held constant, the slope of the curve will still change during the case. This is illustrated by plotting the concentration changes proposed by the two controllers.

A significantly better recovery profile was observed in the closed-loop control group than the manual control group, both for time until opening of the eyes and saying name and birth date. Because of the short duration and homogenous characteristics of the procedure, the differences in recovery times are perhaps clinically less important than found in previous work with longer cases.[10] As BIS nor CePROP were different at the end of the propofol infusion although we found a longer recovery times in the manual control group and more propofol given, the dosing history and its related context sensitive decrement times might be responsible for the differences in recovery profiles.

Before being able to introduce automated control into clinical practice, it has to be proven that it is as clinically feasible as manual control.[22] Therefore, the presence of a control group where a human operator is in charge of controlling a similar system under similar circumstances is essential, as neither well-described criteria nor guidelines are available in the literature. We found that our closed-loop control system resulted in similar hemodynamic and respiratory stability than manual control. Even though some lower MAP was found just after induction, no episodes of severe hypotension nor hypertension were found. Heart rate and saturation remained as stable as in the manual control group. It is important to state that patients remained breathing spontaneously which is challenging for whatever control system. During these procedures, patients were allowed to move their feet, hands, or head. However, the upper legs and pelvis should remain steady as this might result in a short lasting interruption of the retrieval and will upset the gynecologist. Similar results for movement and overall score were found. These results indicate the stability of control under difficult conditions for the operator. It has to be noted that movement response was not and cannot be controlled with a our closed-loop control system, as it depends on the given dose of antinociceptive drugs. At its best, control of the hypnotic component of anesthesia can manage possible arousal reflexes caused by nociceptive stimuli.

It has to be stressed that one should be careful not to extrapolate these results for other patient groups. This was a first feasibility study and as such, we cannot claim full clinical safety, accuracy nor utility. To reach this goal, a large multicenter study is required to investigate the behavior of the system in various populations and specific surgical situations. Additionally, the design and implementation of intelligent alarm systems have to be considered. Although the anesthesiologist in charge of the manual control group has been never involved in the development of this closed-loop system, we accept the possible limitations and bias.

In conclusion, our closed-loop control system titrated propofol administration accurate resulting in BIS values close to the set point and was able to induce the patients within clinical accepted time limits and with less overshoot than the manual control group. Additionally, the overall control system revealed an acceptable robustness. Patients in the closed-loop control group woke up faster. Our closed-loop control group showed to be clinically feasible compared to a manual control group specified by similar hemodynamic, respiratory stability, comparable movement and quality scores.

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